



Letter to Editor

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Association between first trimester tumour necrosis factor- α (TNF- α) levels and miscarriage: A prospective cohort studyMeutia Handiny, Cut Meurah Yeni[✉], Yusra Septivera, Hasanuddin, Niken Asri Utami

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Tumour necrosis factor alpha (TNF- α), a pleiotropic pro-inflammatory cytokine, plays a crucial role in orchestrating immune responses at the maternal-foetal interface. Excessive TNF- α expression can result in compromised implantation, defective placentation, and ultimately miscarriage. Moreover, TNF- α stimulates the release of other inflammatory mediators, creating a feedback loop that exacerbates tissue damage[1]. Despite these insights, limited studies have evaluated TNF- α levels in early pregnancy as a predictive marker in Indonesian populations, particularly in Aceh. Thus, this research aims to explore the relationship between first-trimester TNF- α levels and miscarriage, offering potential clinical utility in early pregnancy risk assessment.

The theoretical foundation of this study rests upon the immunological and inflammatory roles of TNF- α in pregnancy physiology and pathophysiology. During pregnancy, TNF- α contributes to cellular apoptosis, immune modulation, and vascular remodelling required for implantation and placental development[2,3].

We conducted a prospective cohort study between September 2024 and February 2025 at four primary health centres in Banda Aceh: Puskesmas Baiturrahman, Jayabaru, Batoh, and Meuraxa. We recruited pregnant women attending antenatal care using consecutive sampling. Inclusion criteria were: first-trimester singleton pregnancy (<14 weeks gestation), consent to participate, and no known uterine anomalies. Exclusion criteria included metabolic disorders, fibroids, autoimmune diseases, infections, obesity, substance use, and anembryonic pregnancy.

After obtaining informed consent, we collected venous blood samples and transported them into Prodia Laboratory for TNF- α quantification using enzyme-linked immunosorbent assay (ELISA). We followed up each participant until gestational age >20 weeks to determine pregnancy outcomes (either miscarriage or ongoing pregnancy).

We used SPSS version 29.0 for data processing. Due to non-normal distribution of TNF- α levels (Shapiro-Wilk $P < 0.05$), we employed the Mann–Whitney U test for bivariate analysis. A P -value <0.05 was considered statistically significant.

41 pregnant women were included in our study. The mean maternal age was 27 years (range 19–41 years), with 80.5% aged 20–35 years. Most participants had secondary education (58.5%) and were housewives (43.9%). Regarding body mass index (BMI), 53.7% were categorised as normal, 39.0% overweight, and 7.3% underweight. Multigravida accounted for 70.7%, and 19.5% had a history of miscarriage. Of the 41 women analysed, 16 (39.0%) experienced miscarriage in the first trimester. Most miscarriages occurred at 10 weeks gestation (37.5%), followed by 8, 9, and 11 weeks.

Serum TNF- α levels ranged from 0.373 to 4.799 pg/mL. The median value in the miscarriage group was 1.249 pg/mL, compared to 0.814 pg/mL in the ongoing pregnancy group. Bivariate analysis demonstrated a significant difference in TNF- α levels between the two groups ($P = 0.02$), suggesting a positive association between elevated TNF- α and miscarriage risk.

This supports the hypothesis that excessive TNF- α may disrupt foetal–maternal immune tolerance and placental integrity, resulting in pregnancy failure[4,5].

The underlying mechanisms may include TNF- α -induced apoptosis of trophoblast cells and inhibition of human leukocyte antigen G (HLA-G) expression, leading to increased vulnerability of the conceptus to maternal immune attack *via* decidual natural killer (NK) cells[6]. Additionally, TNF- α has been shown to reduce decidualisation and compromise spiral artery remodelling, both of which are essential for normal placental development[6].

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We conclude that elevated serum TNF- α levels in the first trimester are significantly associated with miscarriage. TNF- α may serve as a potential biomarker for predicting adverse pregnancy outcomes and could inform preventive strategies in antenatal care. Larger, multi-centre studies incorporating broader immunological markers are recommended to confirm these findings.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

All authors contributed to the study's conceptualization. Meutia Handiny, Cut Meurah Yeni, Yusra Septivera, Hasanuddin, and Niken Asri Utami were involved in the investigation. The study was designed by Meutia Handiny, Cut Meurah Yeni, Yusra Septivera, Hasanuddin, and Niken Asri Utami. The manuscript was written by Meutia Handiny, Cut Meurah Yeni, Yusra Septivera, Hasanuddin, and Niken Asri Utami.

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